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(54) Title: COMPOSITIONS AND TREATMENT FOR NIGHTTIME PERSISTENT REPRODUCTIVE TRANSITION SYMPTOMS

(57) Abstract

The invention relates to compositions and methods of managing the manifestations of the nighttime symptoms of persistent reproductive transition (or SPRT). A typical composition contemplated by the invention comprises (i) a first active ingredient comprising at least one phytoestrogen, a source of at least one phytoestrogen, or combinations thereof; and (ii) melatonin. Optionally, the composition further comprises a third active ingredient comprising (a) a mixture of remedial carbohydrates including at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least a starch; (b) choline, a source of choline, or combinations thereof; or (c) a combination of (a) and (b).

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COMPOSITIONS AND TREATMENT FOR NIGHTTIME PERSISTENT REPRODUCTIVE TRANSITION SYMPTOMS

1. Field of the Invention

The present invention relates to compositions and methods for alleviating nighttime ailments symptomatic of premenopausal and/or menopausal disorders, associated in some way with an acute, temporary, developing, or chronic imbalance in the serum levels of endogenous, gynecologically relevant substances, including certain neurotransmitters, neurotransmitter substrates and/or hormones. In particular, the present invention relates to compositions comprising at least one phytoestrogen or phytoestrogen derivative, melatonin and, optionally, a mixture of remedial carbohydrates. In a method of the invention, administration of these active ingredients to a subject in need thereof relieves or manages the nighttime disorders, manifestations, conditions, or discomforts complained of.

2. Background of the Invention

Somatic, emotional, metabolic and cognitive difficulties, including sleep problems, night chills and/or sweats, vasomotor symptoms and mood swings, are just some of the symptoms experienced by many menopausal women and also by many premenopausal or perimenopausal women. The severity of the symptoms caused by these reproductive physiological changes may differ among women of various ages (and even within women of approximately the same age). Some women have little or no discomfort, while others become socially and/or physically dysfunctional. In particular, certain women experience difficulties over the course of the night.

For women undergoing menopause, fully 58 percent describe the process as "some-what bothersome", while a

third to one fifth of women found it "very bothersome" depending upon the age of the women reaching menopause. See, *Prevention* (Aug. 1994) 78-142.

The collection of such various aches, irritability, water retention and other complaints experienced to some degree or another by these women whose bodies are in a state of flux can be generally referred to as Symptoms of Persistent Reproductive Transition or SPRT. Most of these ailments manifest themselves mostly during the daytime hours. More specifically, however, a certain set of symptoms are associated with nighttime SPRT, namely, vaginal dryness, libido changes, sleep problems, night chills, night sweats, incontinence (bladder control), and the like. Such nighttime symptoms are particularly troublesome, especially if one or more of these complaints leads to a lack of sleep or adequate rest and potentially compounding the problems experienced by the suffering individual the following day.

The etiology of these reproductive physiological changes is not universally agreed upon. As stated above, SPRT-related changes can affect vasomotor, cognitive, psychological and sexual functions. Some other specific manifestations of women undergoing SPRT include, but are not limited to, weight gain, hot flashes, nervousness, depression, anxiety, vertigo, fatigue, arthralgia, headache, tachycardia, vaginal irritation and heavy bleeding.

It is believed that altered estrogen levels in women may play a significant role in causing SPRT-related ailments. Consequently, Hormonal Replacement Therapy (HRT) has been prescribed as a means to supplement or replace the loss of estrogen commonly observed in women experiencing SPRT-related ailments. The estrogen and endogenous hormones used in HRT, however, have undesirable side effects such as weight gain, excessive bleeding, fluid retention, and increased risk of cancer.

Prevention, vide supra. Moreover, such therapies do little for the nighttime ailments suffered by some of these women. Accordingly, more effective therapies for SPRT-related ailments, particularly the nighttime conditions, are being sought.

There are a number of articles describing the potential treatment of the somatic symptoms of menopausal women by ingestion of foods enriched with phytoestrogens or by ingestion of concentrated forms of phytoestrogens. It has been recognized that the incidence of certain somatic symptoms occurs less frequently in Chinese and Japanese women as compared to women in western countries. Substantial dietary differences exist between these Eastern and Western populations, especially related to the consumption of soy products. Consequently, it has been suggested that the estrogenic effects of phytoestrogens found in soy foods may be responsible for modifying the frequency and severity of somatic symptoms observed in menopausal women in different countries. See, Knight, D. C. et al., in *Obstetrics & Gynecology* (1996) 87:897-904.

2.1.Phytoestrogens

Phytoestrogens are naturally occurring compounds found in many foods and are defined as plant substances that are structurally or functionally similar to estradiol and consist of a number of classes, including lignans, isoflavones, coumestans and resorcylic acid lignans. Recently, a few reports have appeared purporting to observe the alleviation of some somatic symptoms of menopausal women based on the use of the isoflavonoid class of phytoestrogens. These reports, however, continue to focus solely on the use of isoflavonoids as potential agents for modifying estrogen levels to treat somatic symptoms. Most significantly, these references do not teach, disclose, or suggest any benefits to emotional, cognitive, or metabolic symptoms and, most importantly,

fail to teach any benefits for overcoming nighttime symptoms. Nor do these references teach, disclose, or suggest any benefits to the administration or co-administration of melatonin and/or remedial carbohydrates to provide relief to a whole host of SPRT-related ailments, including some of the more problematic nighttime ailments.

Descriptions of methods for treating somatic symptoms of menopausal women by the administration of phytoestrogens exist. Gorbach et al., in U.S. Patent No. 5,498,631, describe a method of treating premenstrual symptoms, menopausal symptoms, or a condition related to reduced levels of endogenous estrogen in women by administering isoflavonoids, which are thought to substitute for the reduced levels of endogenous estrogen. Clearly, Gorbach et al. concentrate on the alleged estrogen-like actions of isoflavonoids. Gorbach et al. make no mention of the potential role of isoflavonoids in a composition or treatment, which also includes effective amounts of melatonin and/or remedial carbohydrates, to alleviate a broader range of daytime or nighttime SPRT-related ailments, including those having a possible etiology in reduced levels of melatonin and/or serotonin. Furthermore, Gorbach et al. do not mention the potential role of phytoestrogens for the treatment of emotional, metabolic, or cognitive disorders and of somatic nighttime disorders.

In U.S. Patent No. 5,506,211 issued to Barnes et al., methods are disclosed for treating patients specifically with the isoflavone genistein to inhibit osteoclastic activity, thereby allegedly preventing osteoporosis. Similarly, Shlyankevich, in U.S. Patent No. 5,424,331, concentrates on the use of phytoestrogens as a means for regulating hormonal levels in women suffering form osteoporosis. Furthermore, Hughes et al., in U.S. Patent No. 5,516,528, describe a composition comprising mammalian

estrogen as a means for regulating hormonal imbalances. Neither Shlyankevich nor Hughes et al. disclose a method for alleviating common nighttime SPRT-related ailments.

2.2.Phytoestrogen Derivatives

Apart from attempting to treat solely the daytime somatic symptoms related to reproductive physiological changes, other references have utilized chemically modified isoflavones, also referred to herein as phytoestrogen derivatives. In U.S. Patent No. 4,390,559, granted to Zilliken, a composition is described using a chemically modified isoflavonoid-like compounds as antioxidants for the preservation of fats and oils. These methods and compositions utilize chemically modified versions of the naturally occurring isoflavone. This patent favors the use of excessive amounts of fats and oils, which may inhibit the beneficial effects of remedial carbohydrates and/or melatonin. Similarly, U.S. Patent No. 5,352,384, granted to Shen, describes a modified isoflavone that is combined with a highly insoluble fiber.

In U.S. Patent 4,557,927, granted to Miyake et al., a process is disclosed for enzymatically converting natural soybean glycosides to an alpha-glycosylated product in which the carbohydrate enzyme substrate is covalently bonded to the phytoestrogen. Similarly, isoflavonoid compounds can be synthesized which resemble the natural isoflavones. In Patent Nos. 4,166,862, 4,163,746, 3,949,085 and 3,864,362, granted to Feuer et al., non-natural isoflavone compounds are synthesized for use as anabolic or catabolic feed additives. Stadler nee Szoke et al., in U.S. Patent Nos. 5,043,326 and 4,826,963, describe a method for the preparation of inclusion complexes of ipriflavon cyclodextrin.

2.3.Melatonin

Melatonin is an endogenous hormone that is produced by the pineal gland. Its regulation has been mentioned, implicated, or failed to be implicated in a wide range of animal and human behavior, including the periodicity of sleep-wake cycles, phase adjustment of circadian rhythms,

mood disorders, secretion of other hormones by prepubertal and pubertal subjects, reentrainment of disrupted sleep in the blind, late afternoon fatigue, insomnia, sedation/hypnosis, jet lag, blood pressure, rectal temperature and the amplification of pulsatile luteinizing hormone.

In U. S. Patent No. 5,449,683, methods of inducing sleep and sleepiness are described comprising the administration of an effective dose of melatonin. The benefits of melatonin, particularly in low doses, are discussed. However, no teaching, suggestion, or disclosure is present on the possible usefulness of exogenously administered melatonin in the management or alleviation of nighttime symptoms of persistent reproductive transition.

2.4.Certain Carbohydrates

Despite a great deal of effort in developing treatments for menopause, there remains an unfulfilled need for a more effective, comprehensive therapy. In particular, as discussed above, prior compositions for treating menopause have involved the use of hormonal replacement therapy, which fall well short of addressing the needs of those women experiencing SPRT-related ailments, especially the nighttime ailments. Quite surprisingly, it has now been found that a more general sense of well-being, as well as other benefits including relief from night sweats, night chills, and the like, is observed through a regimen that affects the imbalances in the body, which imbalances are due not only to hormone or hormone-like substances but also to other substances of gynecological significance, including classes of neurotransmitters.

In mammals, the amino acid tryptophan is the precursor to serotonin synthesis in the brain. Certain carbohydrates, when ingested, can increase the ratio of

tryptophan to large neutral amino acids (T:LNAA) in the blood stream. An increase in the ratio of T:LNAA has been shown to result in a higher level of tryptophan in the brain. A higher level of tryptophan in the brain is believed, in turn, to lead to an increase in the synthesis of endogenous serotonin. While conventional foods (e.g., a potato or a bagel) may fortuitously shift the T:LNAA ratio to a limited extent, these conventional foods also contain fats, sources of protein, other fibers, or may be consumed with other foods that serve as sources of these other components. These other components of conventional foods may slow down digestion, absorption, metabolism and excretion, increase the levels of large neutral amino acids, or otherwise interfere with the desired shift in the balance of specific amino acids in the blood.

It is also important to point out that while a deficiency or imbalance in serotonin levels has emerged as a leading theory behind the symptoms of premenstrual syndrome or PMS (e.g., a number of studies have shown that women with PMS may have a lower serotonin level than women without PMS), such a theory fails to account for or predict the effect of the regulation of serotonin levels (or the levels of other select neurotransmitters, such as dopamine) on premenopausal or menopausal women.

The present invention relates to the discovery that a composition comprising an effective amount of at least one phytoestrogen, in conjunction with an effective amount of melatonin and, optionally, a mixture or blend of remedial carbohydrates can alleviate, treat, or prevent nighttime SPRT-related ailments. In still other compositions of the invention, as discussed below, certain additional benefits obtain from the incorporation of choline or a source of choline to the nighttime preparation.

3. Summary of the Invention

The present invention is directed generally to compositions exhibiting surprising efficacy in alleviating conditions and/or disorders of the type that women experiencing nighttime symptoms of persistent reproductive transition (SPRT) complain of. The present invention is also directed to methods of treating, preventing, inhibiting, managing, ameliorating, or alleviating such nighttime or sleep related symptoms. In particular, relief from the negative effects of the nighttime symptoms or nighttime manifestations, including nighttime somatic, emotional, metabolic, or cognitive disorders, may be achieved through dietary management using the compositions and methods of the invention.

Accordingly, the invention provides a composition for alleviating nighttime symptoms of persistent reproductive transition (SPRT) comprising (i) a first active ingredient comprising at least one phytoestrogen, at least one source of at least one phytoestrogen, at least one phytoestrogen derivative, or combinations thereof and (ii) a second active ingredient comprising melatonin. In other embodiments, compositions are contemplated which further comprise a third active ingredient comprising a mixture of remedial carbohydrates including rapidly digestible, simple, or complex carbohydrates. Selected phytosterols may also be present. In still other embodiments, the third active ingredient may comprise (a) a mixture of remedial carbohydrates including at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least a starch, (b) choline, a source of choline, or combinations thereof, or (c) a combination of (a) and (b).

The amount of melatonin present in the composition of the present invention should be adequate to at least promote sleep and, preferably, should also be effective to alleviate at least one other manifestation of nighttime SPRT. Hence, a unit dose of the contemplated composition

should preferably contain at least about 2 to about 5 mg of melatonin. Lower unit dosages (e.g., less than about 5 mg) are suitable, including but not limited to about 1 mg or less, less than 1 mg, about 0.5 mg or less, about 0.3 mg, or as low as about 0.1 mg. More preferably, the a unit dose of the composition provides an amount of melatonin which on administration to a subject is effective to raise the circulating blood, serum, or plasma level of melatonin in the subject to the normal nocturnal physiological blood, serum, or plasma levels of normal individuals. Most conveniently, the composition comprising melatonin is administered when sleep is desired, or within about two hours of when sleep is desired, preferably, within about one hour or less, more preferably within about thirty minutes of when sleep is desired. Hence, in a specific embodiment of the invention the administration of the phytoestrogen and/or melatonin is carried out on or before bedtime (or sleep time), preferably, within about two hours before bedtime.

It is important to note that the use of the terms "bedtime", "nighttime", "sleep related", or "nightly" should be construed broadly to encompass what particular individuals or groups of individuals consider their bedtime, nighttime, sleep related, night, or alternatively, "sleep time." That is, certain individuals, such as shift workers, nurses, medical or emergency workers and/or technicians, and the like, may consider their bedtime, nighttime, sleep related, night, or sleep time to be something other than the conventional meanings of these terms. Some may sleep during the early evenings and "arise" for a graveyard shift. Still others may only sleep in the wee hours of the morning and early morning. Hence, the terms bedtime, nighttime, sleep related, nightly, or sleep time are meant to encompass the conventional meanings of these terms, as well as what a particular user of the invention may consider to be the

preferred time periods for sleep and rest appropriate for that user and during which some of the "nighttime" or "sleep related" symptoms may become manifest.

The invention also provides a method of alleviating the negative effects of nighttime symptoms of persistent reproductive transition (SPRT) comprising administering to a subject in need thereof an effective amount of at least a first substance comprising at least one phytoestrogen, at least one source of at least one phytoestrogen, at least one phytoestrogen derivative, or combinations thereof and an effective amount of at least a second substance comprising melatonin. Consistent with a method of dietary management, first, second, or both substances are preferably administered with a carrier, more preferably a nutritionally acceptable carrier, most preferably an edible solid, edible semi-solid, or edible liquid carrier.

The invention also contemplates a method that alleviates the negative effects of symptoms of persistent reproductive transition (SPRT) relating to nighttime somatic disorders, comprising administering to the subject in need thereof an effective amount of at least one phytoestrogen, at least one source of at least one phytoestrogen, at least one phytoestrogen derivative, or combinations thereof.

In a particular embodiment, the method contemplated further comprises administering an effective amount of melatonin and, optionally, a blend of two or more remedial carbohydrates, preferably a mixture of at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least one remedial starch. More preferably, the method further comprises administering an effective amount of choline or a source thereof. Any route of administration can be taken. However, the oral (by mouth) or topical (transdermally, intravaginally, or the like) route is preferred. Moreover, each active

component can be administered sequentially, preferably within about an hour of each other, or substantially concurrently. Administration of effective amounts of the active ingredients is preferably carried out for as long as the nighttime SPRT symptoms persist.

It has surprisingly been discovered that the compositions and methods of the invention provide great benefits to women who experience a whole range of discomforts associated with nighttime SPRT. Such benefits include relief from, for example, nighttime somatic, emotional, metabolic, or cognitive associated ailments. It is believed that the compositions and methods of the invention provide relief from the nighttime symptoms by supplying particular nutrients, including a combination of selected substances, having the capacity to correct (through a regimen of dietary management) adverse physiological, psychological and psychiatric states stemming from alterations primarily in endocrine synthesis and secretion accompanying a woman's approach, progression and passage through a post reproductive stage during her later years of life.

To name some of the specific benefits observed from the administration of the compositions or implementation of the methods of the invention to subjects suffering from nighttime SPRT-related ailments include, but are not limited to, inhibition of vaginal dryness, changes in (particularly a reduction of) libido, sleep problems, night chills, incontinence, night sweats, and elimination of need for concurrent hormone replacement therapy. In other instances, it has also been observed that subjects receiving treatment experience an improvement in mood, less water retention, less irritability, or an increased ability to concentrate or remain mentally alert during the "daytime" hours.

Hence, in a specific embodiment of the invention, a useful composition is disclosed for the dietary management

of nighttime SPRT-related ailments, comprising at least one phytoestrogen, a source of at least one phytoestrogen, or combinations thereof and melatonin. Optionally, the composition further comprises a mixture of blend of remedial carbohydrates. In another embodiment, the composition of the invention further comprises an amount of choline sufficient to inhibit or reverse episodes of cognitive deficit or decline, including lack of alertness or an inability to maintain premenopausal functionality, in those females unsettled by nighttime symptoms of persistent reproductive transition.

In still another embodiment, a composition is described which comprises a combination of at least one phytoestrogen, a source of at least one phytoestrogen, or combinations thereof, melatonin and an effective amount of choline, a source of choline, or combinations thereof, independent of the presence of an effective amount of a mixture or blend of selected remedial carbohydrates.

Hence, the invention contemplates methods of using therapeutic and/or nutritional compositions for alleviating, treating, preventing, ameliorating, or managing the adverse effects of nighttime SPRT-related ailments. Broadly, such methods comprise administering a therapeutically or nutritionally effective amount of the composition to subjects in need thereof.

Other objects of the invention will become apparent to those of ordinary skill in the art upon further consideration of the entire disclosure provided herewith.

4. Glossary of Terms

The following terms appear in the present specification and are defined as follows:

Symptoms of Persistent Reproductive Transition or SPRT - A collection of symptoms, manifestations, disorders, complaints, discomforts, or aches and pains which is experienced by perimenopausal or premenopausal

women, menopausal women, or postmenopausal women. See, Table 1, below, in which symptoms are categorized as somatic, emotional, metabolic, cognitive, or nighttime symptoms. In particular, a subject suffering from nighttime SPRT or a nighttime SPRT-related ailment is a woman having at least one of the nighttime symptoms listed in Table 1, below. Additionally, a subject suffering from at least one of the nighttime symptoms may also be suffering from at least one other, perhaps at least two, three, or more other, non-nighttime symptoms.

TABLE 1. ILLUSTRATIVE DISORDERS/SYMPTOMS/MANIFESTATIONS ASSOCIATED WITH SPRT

I. Somatic
- vaginal dryness
- hot flashes
- fluid retention
- breakthrough bleeding
- excessive bleeding
- vertigo
- headache or migraines
- tachycardia
- libido changes (loss of sexual drive)
- sleep problems
- joint pain
- frequent urination (incontinence)
- breast tenderness
- chills
- cold sweats (night sweats)

II. Emotional
- irritability
- anxiety
- lack of energy (lethargic)
- fatigue
- mood changes (depressed mood, mood swings)

III. Metabolic
- weight gain
- marked change in appetite (increased or decreased)
- arthralgia (muscle ache)
- carbohydrate craving
- greater tendency to incur a bone fracture

IV. Cognitive
- forgetfulness
- recall or short term memory loss
- loss of alertness
- inability to concentrate

V. Nighttime or Sleep Related Symptoms
vaginal dryness
libido change
sleep problems
chills
incontinence (bladder control)
night sweats

The sub-category of sleep problems may relate to difficulty in initially falling asleep, waking up one or more times during the night, difficulty in falling back asleep once awakening during the night, lack of quality sleep (e.g., a fitful sleep), a feeling of grogginess in the morning, and the like.

Another subject in need of treatment, who may benefit from the invention, is a woman having episodic or chronic manifestations of at least one of the recited nighttime SPRT-related conditions (ailments, disorders and the like) and who is also experiencing changes or irregularities in her menstrual flow or cycle attributable to perimenopausal, menopausal, or postmenopausal transition. It is important to note, however, that some of the same symptoms, which are listed in Table 1, can be induced through the administration of, intake of, or exposure to pharmacological agents, chemicals, hormones and the like, or through accident, trauma, or surgery (e.g., loss or removal of some portion of the reproductive system, such as the uterus and/or one or both ovaries).

Remedial carbohydrates - Simple or complex carbohydrates, including certain forms of starch, which are rapidly digestible and which on consumption increases serotonin levels in the blood, serum, plasma, or synaptic structure(s) relative to the levels of this substance in the blood, serum, plasma, or synaptic structure(s) prior to the consumption of the remedial carbohydrate. That is, consumption of these remedial carbohydrates increases the level of endogenous serotonin synthesis. Examples of such remedial carbohydrates include, but are not limited to,

dextrose, galactose, mannose, dextrin, maltodextrin, cyclodextrin, potato starch, pre-gelatinized starch, gelatinized starch, fructose, sucrose, maltose, maltotriose, maltotetraose, or mixtures thereof. It should be pointed out that the remedial carbohydrates, which are suitable for use in the invention, are substances, naturally derived or otherwise, which are deliberately added (as an admixture) to the other components of the compositions of the present invention. That is, carbohydrates, such as conventional flour, that may be naturally present in certain foodstuffs are not considered to be remedial carbohydrates. In addition, a mixture or blend of two or more, perhaps three or more, remedial carbohydrates refers to a physical combination or admixture of two, three, or more distinct types of remedial carbohydrates. In preferred embodiments of the invention, a mixture comprising at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least one remedial starch may be utilized.

Phytoestrogens - Substances that belong to a family of compounds that are naturally found in certain plants (a natural source), including foodstuffs, especially soy and soy products. Soy proteins are a convenient source of phytoestrogens, especially soy phytoestrogens. Examples of phytoestrogen compounds include, but are not limited to, lignan, genistein, daidzein, Biochanin A, formononetin, O-desmethylangolensin, glycetein, texasin, equol, prunetin, apegenin, coumestrol, saponaretin, 7-hydroxyisoflavone, 5,7-dihydroxyisoflavone, 7,4-dihydroxyflavone, 6,7,4'-trihydroxyisoflavone, or their natural glycosylated (e.g., genistein 7-D-glucoside), acetylated, or methoxylated (e.g., genistein 4'-methyl ether) forms. Phytoestrogens can occur and be used either as the aglycon (i.e., minus the sugar moiety), ester, ether, or as the glycosylated form (i.e., glycosides).

Examples, of phytoestrogen glycosides include, but are not limited to, genistin, daidzin, glycetin, saponarin and the like. Naturally obtained phytoestrogens can, of course, be prepared synthetically (i.e., by total synthesis) or semi-synthetically (e.g., by using a natural product as a starting material and subsequently modifying same) using conventional synthetic methods.

In keeping with the desire to substantially utilize only naturally occurring active components, substantially unmodified phytoestrogens obtained from their natural sources are preferred. However, the total synthetically or semi-synthetically prepared natural phytoestrogens, phytoestrogen derivatives and/or analogs may also be used to advantage herein. Such derivatives or analogs of phytoestrogens may also be referred to herein simply as "phytoestrogen derivatives."

Choline or a Source of Choline - These terms refer to the substance choline or 2-hydroxy-N,N,N-trimethyl-ethanaminium [$HOCH_2CH_2N^+(CH_3)_3$], to choline salts, typically as its halide (e.g., fluoride, chloride, bromide or iodide) or hydroxide salt, or to a substance, which when broken down in the body increases circulating levels of choline. Examples of substances that provides a source of choline *in vivo*, include but are not limited to citicoline or CDP-choline, phosphatidyl choline and the like. Certain foods or foodstuffs may also provide a source of choline, including but not limited to, animal and plant products, such as bile, brains, lecithin and the like, egg yolks, hops, barley, belladonna, or strophanthus.

Phytosterols - Substances having a steroidal backbone or nucleus and which may be isolated from plants. An example, includes alpha-sitosterol, beta-sitosterol, gamma-sitosterol, campesterol, stigmasterol, delta-5-avennasterol, delta-7-stigmasterol, brassicasterol, lupenol, alpha-spinasterol, or the like. Phytosterols may

be present naturally in certain foods and foodstuffs, which may form part of the compositions of the present invention. Phytosterols may also be deliberately added.

5. Detailed Description of the Preferred Embodiments

One of the principal ingredients of the instant compositions, phytoestrogens, is generally available as isoflavones and can be obtained from soy proteins, soybeans, vegetable protein, tempeh, tofu, miso, aburage, atuage, or koridofu. Preferred phytoestrogens include, but are not limited to, genistein, daidzein, glycetin or a combination thereof. As mentioned above, the remedial carbohydrate mixture or blend constitutes an admixture of two or more, preferably three or more, different types of remedial carbohydrates. Preferred types of remedial carbohydrates include, but are not limited to, dextrose, dextrin, maltodextrin, mannose, pre-gelatinized starch, gelatinized starch and starch, particularly potato starch. Choline or a source thereof can be obtained from any combination of lecithin, choline chloride, choline bitartrate and choline dihydrocitrate. Choline, itself, comprises free choline, its salt, ester, acid, or synthetic or natural conjugate (e.g., CDP-choline, phosphatidyl choline and the like).

In one embodiment of the invention compositions are provided which comprise at least one phytoestrogen in an admixture with at least a second active component comprising melatonin and, optionally, at least a third active component selected from (i) a mixture or blend of remedial carbohydrates, (ii) choline or a source thereof, or (iii) both carbohydrates and choline.

A preferred composition comprises an admixture of (a) about 20-100 g of soy protein (preferably, about 20-80 g or more preferably, about 30-60 g) comprising about 20-55 mg, preferably about 30-45 mg, of soy isoflavones (i.e., one or more phytoestrogens or phytoestrogen derivatives)

and about 0.1-10 g melatonin (preferably, about 0.1-5 mg or more preferably, about 0.1 to about 1 mg). Melatonin derivatives and/or analogs may also be used in place of melatonin. Such derivatives and/or analogs are well known to those of ordinary skill in the art. See, e.g., U. S. Patent No. 5,403,851, the complete disclosure of which is incorporated by reference herein. Hence, any use of the term "melatonin" herein is meant to encompass known derivatives and/or analogs thereof.

The preferred embodiment of the invention may optionally comprise about 20-80 g of the remedial carbohydrate mixture or blend comprising about 25-45% of dextrose, about 40-70% of maltodextrin and about 1-10% of potato starch by weight of total remedial carbohydrate. Furthermore, the composition may also comprise about 0-5 g of choline, preferably about 1-3 g.

A specific composition of the invention comprises a unit admixture of (a) about 60 g of soy protein comprising at least about 14 to about 27 mg of genistein and at least about 12 to about 18 mg of daidzein, (b) less than about 1 mg of melatonin, preferably about 0.3 or about 0.5 mg. A third active component may be present, namely, about 50 g of a remedial carbohydrate mix comprising about 37% of dextrose, about 60% of maltodextrin and about 3% of potato starch by weight of total remedial carbohydrate. Yet a fourth active component may be present, namely, about 1 g of free choline. As discussed above, the genistein and daidzein can be replaced by genistin and daidzin, either individually or together.

Preferably, the compositions provided are combined with a carrier, more preferably a nutritionally acceptable carrier, such as an edible solid, semi-solid, or liquid carrier, including in the form of dietary product, food, food snacks, or drink, to name a few. Preferred carriers may include sorbet, sherbet, apple sauce, or pudding. Hence, the compositions contemplated can come in many

forms including, but not limited to, a dry powder, liquid concentrate, ready-to-drink, ready-to-eat, cold, ambient, hot, beverage or prepared food, e.g., a flavored drink (tea, milk, chocolate and the like) or nighttime snack (cookie, biscuit, mint, candy and the like). Other food products may also be contemplated including cereal, cereal additive (sprinkled on), pastry or baked goods (pop tart, cracker, cake, muffin), pudding or food bar, frozen product (pop tart, ice cream), cake mix, or spread.

Another embodiment of the invention is directed to a method for managing, treating, alleviating, or preventing nighttime somatic, emotional, metabolic, or cognitive disorders experienced by premenopausal, menopausal, or postmenopausal women by administering to the subject an effective amount of at least one phytoestrogen, at least one source of phytoestrogen, at least one phytoestrogen derivative, or combinations thereof. Preferable, the subject in need of such treatment is administered about 30-60 g of soy protein, which includes about 30-45 mg of isoflavones. In addition, the subject is administered an effective amount of melatonin (or derivative and/or analog thereof). Most preferably, the subject is administered about 60 g of soy protein, which includes about 27 mg of genistein and about 18 mg of daidzein, and a submilligram dose of melatonin.

When the composition or method of the invention calls for the presence of remedial carbohydrates, simple carbohydrates may be selected from dextrose, galactose, mannose, fructose, sucrose, maltose, or mixtures thereof, while complex remedial carbohydrate may be selected from dextrin, maltodextrin, cyclodextrin, maltotriose, maltotetraose, or mixtures thereof. The remedial starch may be in turn selected from potato starch, pre-gelatinized starch, gelatinized starch, or mixtures thereof.

The subject in need of such treatment is administered the therapeutic, dietary, or nutritional composition once or twice nightly, preferably at or around bedtime or sleep time. The composition can be administered additionally in the early evening, if the composition is taken more than once "nightly." If the composition is administered more than once a night, the administrations are preferably separated by about two to about eight hours, preferably, about three to about six hours, more preferably about four to about five hours. The regimen may last for only a day, a few days, or it may continue for as long as the symptoms persist (e.g., daily for 365 days of the year). More typically, however, the regimen may last anywhere from a period of about one week, two weeks, three weeks, or four weeks to a period of about one month, two months, three months, four months, five months, six months, or at least a year.

In yet another embodiment of the invention, a method is described for managing, treating, alleviating, or preventing in a subject suffering from a nighttime SPRT-related condition, which method comprises administering to the subject in need thereof an effective amount of at least one phytoestrogen, at least a second component comprising melatonin, at least a third component comprising a mixture or blend of remedial carbohydrates and at least a fourth component comprising choline or source thereof. A preferred method comprises administering to the subject an admixture of (a) about 100 g of soy protein comprising at least about 50 mg of genistin and about 30 mg of daidzin, (b) about 0.1 to about 1.0 mg melatonin, (c) about 50 g of a remedial carbohydrate mix comprising about 35-40% of dextrose, about 50-60% of maltodextrin and about 1-5% of potato starch by weight of total remedial carbohydrate, and (d) about 1-2 g of a choline salt.

The ultimate amount of phytoestrogen, melatonin, carbohydrates, and/or choline administered will ultimately vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms, including the nighttime and non-nighttime symptoms; the kind of concurrent treatment; and the effect desired.

As stated above, the therapeutic compositions can be prepared in the form of a ready-to-use dietary product or in the form of a dietary product concentrate. Ready-to-use products include, but are not limited to, prepared foods such as a beverage, pastry, baked goods, pudding, food bar, or frozen product. Concentrated forms include, but are not limited to a dry powder, liquid concentrate, cereal additive, cake mix, candy, or spread.

To further illustrate the invention, specific examples are provided herewith.

6. Examples

6.1.A Typical Formulation

An edible composition is prepared from a combination of about 20-140 g (preferably about 40-100 g) of soy proteins, including about 20-90 mg (preferably about 30-55 mg) of naturally present or added isoflavones, and about 0.1 to about 10 mg, preferably 5 mg or less of melatonin. The edible composition of the invention optionally further comprises about 20-80 g of a mixture of remedial carbohydrates. Preferred compositions comprises about 60-120 of soy protein, including about 45-90 mg of isoflavones, and about 0.3 to about 0.9 mg melatonin. The total weight of the edible composition can range from about 40 g to about 200 g. The composition may in addition contain at least two, preferably at least about three, four, or more different types of remedial

carbohydrates selected from dextrose, dextrin, maltodextrin, mannose, gelatinized starch, pre-gelatinized starch, rice starch and potato starch. The edible compositions may further contain about 0.5-5 g of choline or a source of choline in place of the remedial carbohydrates or in addition to the remedial carbohydrates.

6.2.A Powder Suitable for Reconstitution to a Beverage

A dry powder is prepared comprising phytoestrogen, carbohydrate mix and choline, as follows: soy proteins (60 g), isoflavones (45 mg, in the form of genistein, 27 mg, and daidzein, 18 mg), melatonin (0.5 mg), carbohydrate mix (50 g, comprised of dextrose, 18.5 g, maltodextrin, 30 g, and starch, 1.5 g), choline (1 g). This powder can be mixed with about 8-24 oz. of water to provide a hot or cold beverage.

6.3.A Ready-To-Drink Beverage

A flavored beverage is prepared comprising about 8-12 oz. of flavored water mixed with phytoestrogen, melatonin, carbohydrate blend and choline, as follows: soy proteins (55 g), isoflavones (60 mg, in the form of genistin, 35 mg, and daidzin, 25 mg), melatonin (0.9 mg), carbohydrate blend (60 g, comprised of dextrose, 20 g, maltodextrin, 30 g, and starch, 10 g), choline (1.5 g).

6.4.A Baked Muffin

Baked muffins are prepared by adding to two cups BISQUICK, 1 cup milk, and 1 whole egg, a dry powder comprising phytoestrogen, melatonin, carbohydrate mix and choline, as follows: soy proteins (60 g), isoflavones (45 mg, in the form of genistein, 27 mg, and daidzein, 18 mg), melatonin (0.7 mg), carbohydrate mixture (50 g, comprised of dextrose, 18.5 g, maltodextrin, 30 g, and starch, 1.5 g), choline (1 g). After blending, the batter is poured

into muffin molds and baked in the oven at a temperature of about 300-350 degrees Fahrenheit for about 15-30 minutes.

6.5.A Powder Suitable for Reconstitution to a Beverage

A dry powder is prepared comprising phytoestrogen and choline, as follows: soy proteins (65 g), isoflavones (50 mg, in the form of genistein, 28 mg, and daidzein, 22 mg), melatonin (1 mg) and choline chloride (3 g). This powder can be mixed with about 8-24 oz. of water to provide a beverage providing phytoestrogens, melatonin and choline.

6.6.Rice Pudding

Rice pudding is prepared by adding to two cups rice pudding mix, 1 cup milk, and 1 whole egg, a dry powder comprising phytoestrogen, melatonin, carbohydrate mixture and choline, as follows: soy proteins (90 g), isoflavones (70 mg, in the form of genistin, 40 mg, and glycetin, 30 mg), melatonin (0.3 mg), carbohydrate mixture (50 g, comprised of mannose, 18.5 g, maltotriose, 30 g, and pre-gelatinized starch, 1.5 g), citicoline (1.5 g). After blending, the smooth batter is poured into paper cups and refrigerated for about 30 minutes to about 1 hour prior to consumption.

6.7.Treatment of Subject No. 1

A subject suffering from an emotional, metabolic, or cognitive disorder in addition to at least one of the nighttime symptoms is given a reconstituted beverage obtained from the powder described in Example 6.5 once a night administered in the evening. The nightly dosing is continued for approximately 90 days. Improvement in the alleviation of the complained of symptoms is observed after about one month from the start of the regimen. After the three month period, the subject reports complete

relief from fatigue, anxiety, bouts of forgetfulness and any sleep problems.

6.8.Treatment of Subject No. 2

A subject suffering from any one or a combination of nighttime SPRT-related conditions is treated by the administration of an admixture of (i) phytoestrogens in the form of 60 g of soy protein containing 45 mg of soy isoflavones (in turn containing 27 mg genistein and 18 mg daidzein); (ii) less than about 1.0 mg melatonin; (iii) 20-80 g of a mixture of remedial carbohydrate including approximately 25 to 45% of dextrose, 40 to 70% of maltodextrin and 1 to 10% of potato starch; and (iv) approximately 0.5 To 5.0 g of free choline (base) or the calculated equivalent as a choline salt, ester, acid or synthetic or natural conjugate. The admixture is administered once or twice nightly, preferably administered between a 6 p.m. and midnight for period for 365 days per year or as long as symptoms of nighttime SPRT persist. When administered twice a night, the composition is given in the early evening and again before bed.

6.9.Treatment of Subject No. 3

A subject suffering from a nighttime SPRT-related conditions is given approximately 50 g of remedial carbohydrate blend containing approximately 37% of dextrose, 60% of maltodextrin and 3% of potato starch administered in conjunction with a choline source, phytoestrogen source and melatonin. The compositions is administered twice a night, as needed, preferably in the early evening or just before bed and again during the night, if an episode of sleep problems and or any of the other nighttime symptoms of the subject causes the subject to awaken. This regimen is carried out for about six months or as long as the nighttime SPRT-related symptoms persist.

6.10.Treatment of Subject No. 4

A subject suffering from weight gain, lapses in memory and night sweats is treated by receiving approximately 1.0 g of free choline administered in conjunction with a remedial carbohydrate blend, phytoestrogen source and melatonin according to the muffin of Example 6.4. The muffin is administered once nightly, preferably within half an hour of bedtime or sleep time for 255 days. The subject is symptom free after the treatment period.

Hence, the foregoing examples illustrate the successful management, through the administration of a diet of nutritional supplements, of a wide range of symptoms, especially nighttime symptoms, associated with perimenopausal, menopausal, or postmenopausal ailments experienced by women in their middle to late years of life.

It should be apparent to those of ordinary skill in the art that other embodiments of the invention may be readily contemplated in view of the teachings of the present specification. Such embodiments, although not specifically disclosed, nevertheless fall within the scope and spirit of the invention. Hence, the invention should not be construed as being limited to the specific embodiments provided, which invention is limited solely by the claims that follow.

WHAT IS CLAIMED IS:

1.A composition for alleviating nighttime symptoms of persistent reproductive transition (SPRT) comprising (i) a first active ingredient comprising at least one phytoestrogen, at least one source of at least one phytoestrogen, at least one phytoestrogen derivative, or combinations thereof and (ii) a second active ingredient comprising melatonin.

2.The composition of claim 1 which further comprises a third active ingredient comprising a mixture of remedial carbohydrates including rapidly digestible, simple, or complex carbohydrates.

3.The composition of claim 1 which further comprises a third active ingredient comprising (a) a mixture of remedial carbohydrates including at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least a starch, (b) choline, a source of choline, or combinations thereof, or (c) a combination of (a) and (b).

4.The composition of claim 1 which further comprises a nutritionally acceptable carrier.

5.The composition of claim 4 in which said carrier comprises an edible solid or semi-solid carrier.

6.The composition of claim 4 in which said carrier comprises an edible liquid carrier.

7.The composition of claim 1 in which said phytoestrogen comprises a soy phytoestrogen.

8.The composition of claim 1 in which said phytoestrogen is obtained from its natural source or from a synthetic or semi-synthetic process.

9.The composition of claim 1 in which said phytoestrogen derivative is obtained from a total synthetic or semi-synthetic process.

10.The composition of claim 7 in which said phytoestrogen is obtained from soybean or a soy product selected from tofu, miso, aburage, atuage, or koridofu.

11.The composition of claim 1 in which said phytoestrogen comprises genistin, daidzin, glycetin, or saponarin.

12.The composition of claim 1, a unit dose of which provides an amount of melatonin which is about 5 mg or less.

13.The composition of claim 1, a unit dose of which provides an amount of melatonin which is about 1, about 0.7, about 0.5, or about 0.3 mg.

14.The composition of claim 1, a unit dose of which provides an amount of melatonin which is less than 1 mg.

15.The composition of claim 1, a unit dose of which provides an amount of melatonin which on administration to a subject is effective to raise the circulating blood, serum, or plasma level of melatonin in said subject to the normal nocturnal physiological blood or plasma levels of normal individuals.

16.The composition of claim 2 in which said remedial carbohydrates on consumption increases the level of endogenous serotonin synthesis.

17.The composition of claim 2 in which the third active ingredient comprises a blend of two, three, or more remedial carbohydrates.

18.The composition of claim 1 which contains about 20 to about 100 g of soy protein.

19.A method of alleviating the negative effects of nighttime symptoms of persistent reproductive transition (SPRT) comprising administering to a subject in need thereof an effective amount of at least a first substance comprising at least one phytoestrogen, at least one source of at least one phytoestrogen, at least one phytoestrogen derivative, or combinations thereof and an effective amount of at least a second substance comprising melatonin.

20.The method of claim 19 which further comprises administering an effective amount of at least a third substance comprising a blend of two or more remedial carbohydrates, choline, a source of choline, or combinations thereof.

21.The method of claim 19 which further comprises administering an effective amount of at least a third substance comprising (a) a mixture of remedial carbohydrates including at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least one remedial starch, (b) choline, a source of choline, or combinations thereof, or (c) both (a) and (b).

22.The method of claim 19 in which the first, second, or both substances are administered with an edible carrier.

23.The method of claim 19 in which the administration step is carried out on or before bedtime.

24.The method of claim 19 in which the administration step is carried out within about two hours before bedtime.

25.The method of claim 19 in which the administration step is carried out nightly for a period of about one week, two weeks, three weeks, or four weeks.

26.The method of claim 19 in which the administration step is carried out nightly for a period of about one month, two months, three months, four months, five months, six months, or at least a year.

27.The method of claim 19 in which the administration step is carried out once nightly.

28.The method of claim 19 in which the administration step is carried out twice nightly.

29.A method of alleviating the negative effects of symptoms of persistent reproductive transition (SPRT) relating to nighttime disorders, comprising administering to the subject in need thereof an effective amount of at least one phytoestrogen, at least one source of at least one phytoestrogen, at least one phytoestrogen derivative, or combinations thereof.

30.The method of claim 29 which further comprises administering an effective amount of melatonin.

31.The method of claim 30 which further comprises administering an effective amount of a blend of two or more remedial carbohydrates.

32.The method of claim 30 which further comprises administering an effective amount of a mixture comprising at least one simple remedial carbohydrate, at least one complex remedial carbohydrate and at least one remedial starch.

33.The method of claim 32 which further comprises administering an effective amount of choline, a source of choline, or combinations thereof.

34.The method of claim 32 in which the administration step is carried out orally.

35.The method of claim 31 in which the administration step is carried out for as long as the nighttime SPRT symptoms persist.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/20964

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A01N 33/12, 65/00, 43/16, 47/40
US CL :514/60, 456, 642, 514
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/60, 456, 642, 514

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE, AGRICOLA, WPIDS
Search terms: phytoestrogen, estrogen, menopause, PMS, premenstrual, melatonin, genistein, genistin, saponarin, glycetin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,424,331 A (SHLYANKEVICH) 13 JUNE 1995. See whole document.	1-35
Y	US 5,498,631 A (GORBACH et al.) 12 MARCH 1996. See whole document.	1-35
Y	US 3,949,085 A (FEUER et al.) 06 APRIL 1976. See whole document.	1-35
Y	US 4,166,862 A (FEUER et al.) 4 SEPTEMBER 1979. See whole document	1-35
Y	US 4,746,674 A (PIERPAOLI et al.) 24 MAY 1988. See column 3, columns 4 and 9.	1-35

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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16 JANUARY 1998

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/20964

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,516,528 A (HUGHES et al.) 14 May 1996. See entire document, especially Table I, column 10.	1-35